A SINGLE ARM, OPEN-LABEL, MULTI-CENTER, INTERVENTIONAL STUDY EVALUATING THE EFFICACY AND SAFETY OF CEFTAZIDIME-AVIBACTAM (CAZ-AVI) IN CHINESE ADULTS WITH HAP (INCLUDING VAP)

CCI [redacted]

Study Intervention Name:	Ceftazidime - Avibactam
US IND Number:	N/A
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Phase:	4

Short Title: Efficacy and Safety of Ceftazidime-Avibactam (CAZ-AVI) in Chinese Participants With HAP (Including VAP)

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	**07 February 2022**	• Added "CT scan" in Disease characteristics of Section 1.3 SoA, footnote "g" and Section 5.1 Inclusion Criteria 4 as an acceptable standard of care in assessing presence of pulmonary infiltration to incorporate the PACL (version date 18 Dec 2020). • Rephrased the test frequency of estimated creatinine clearance on Visits 3-15 in Section 1.3 SoA and footnote "p", "s" to keep consistent with that of serum creatinine so as to keep in line with amikacin prescription information. • Added wording of "If Day 1 and Screening Visit occur on the same calendar day, lab results from Screening Visit can be used on Day 1 visit" on Section 1.3 SoA footnote "o" to clarify the requirement when Day 1 and Screening Visit occur on the same calendar day. • Wording change of "a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the CAZ-AVI" to "a second pregnancy test will be required at the baseline visit prior the participant's receiving the CAZ-AVI." in Section 1.3 SoA footnote "q" and Section 8.2.4 Pregnancy Testing to keep consistency throughout the protocol. • Wording change of Inclusion Criteria 3 from "Onset of symptoms ≥48 hours after admission or <7 days after discharge from an inpatient acute or chronic care facility" to "Onset of signs and symptoms (including Inclusion Criteria 4, 6, and 7) ≥48

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		hours after admission or <7 days after discharge from an inpatient acute or chronic care facility" in Section 5.1 Inclusion Criteria to clarify the required time window of signs and symptoms onset. • Added wording "prior enrollment" to clarify time frame of previous antibiotic exposure before enrollment in Exclusion Criteria 9 of Section 5.2 Exclusion Criteria. • Wording change of "Acute Physiology and Chronic Health Evaluation (APACHE) II score >30 or <10 using the most recent available data" to "Acute Physiology and Chronic Health Evaluation (APACHE) II score >30 or <10 using the available data within 24 hours prior baseline" to clarify the requirement of time window of data used to calculate APACHE II score. • Wording change of "carbapenems and CAZ-AVI" to "carbapenems and/or CAZ-AVI" to clarify targeted population in the study to keep consistent of study population with Ph3 study. • Wording change of dose formulation in Section 6.1 Study Intervention(s) Administered from "lyophilized powder for solution for injections" to "powder for solution for injections" to be in line with CAZ-AVI label and to incorporate content of PACL (version date 21 Jul 2021). • Added a footnote for Table 1 "Time windows of dose frequency are Q8H ± 30mins, Q12H ± 30mins, Q24H ± 30mins and time window of infusion time is 2 hours ± 10mins" in Section 6.1.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Changed requirement of blood glucose test from "fasting" to "non-fasting" in Section 10.2 Appendix 2: Clinical Laboratory Tests. Because participant may be screened at any time of the day of Screening Visit and it is needed that participant receive IMP as soon as possible after eligibility is confirmed. Local lab results at baseline can be lab results from Screening Visit if Screening Visit and baseline occur on the same calendar day. • Added footnote "HCO_3 or CO_2-CP results in blood chemistry will be assessed only for those participants at sites which can perform the HCO_3 or CO_2-CP tests." of HCO_3 / CO_2-CP in Section 10.2 Appendix 2: Clinical Laboratory Tests to incorporate content of PACL (version date 21 Jul 2021). • Added APACHE II Score Worksheet used for calculation when different units of test results generated by local lab and related formulas.
Original protocol	2 September 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letter.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Efficacy and Safety of Ceftazidime-Avibactam (CAZ-AVI) in Chinese Participants With HAP (Including VAP)

Rationale

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after admission, without being in the incubation period of infection at the time of admission. Ventilator-associated pneumonia (VAP) is a sub-type of HAP and is defined as pneumonia that occurs 48 hours or more after mechanical ventilation in patients undergoing endotracheal intubation or tracheotomy[1]. In the United States (US), the incidence of hospital-acquired infections in hospitalized patients was 4%, of which pneumonia accounted for approximately 21.8%[2]. According to the results of a cross-sectional survey of large-scale nosocomial infection in China, the incidence of hospital-acquired infections in hospitalized patients was approximately 3%-5%, among which the incidence of hospital-acquired lower respiratory tract infection was approximately 2%[3,4].

The most common resistant Gram-negative pathogens causing HAP/VAP in China include extended spectrum β-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)[1]. Currently the options for the treatment of Gram-negative infections, especially multidrug resistant strains including extended-spectrum β-lactamases (ESBL) producers, are extremely limited. Hence, availability and development of new agents to treat these infections will be welcome addition to the existing treatment.

In China, CAZ-AVI was approved by the National Medical Products Administration (NMPA) on 21 May 2019. Indications for adults approved include complicated intra-abdominal infection (cIAI), HAP (including VAP), and for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.

This study is designed to CCI [redacted] to further evaluate effectiveness of CAZ-AVI in Chinese patients with HAP, including VAP. CCI [redacted].

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To estimate clinical response to CAZ-AVI in HAP patients.	• Using a composite estimand strategy to estimate the clinical response rate at the test of cure (TOC) visit in participants who meet minimum disease requirements (excluding participants not expected to respond to CAZ-AVI). Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before TOC visit where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering treatment with further antibiotics will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and TOC visit inclusive, development of infectious complications of pneumonia after Day 2 until TOC visit triggering treatment with further antibiotics will be regarded as failure clinical response.	• The proportion of participants with clinical cure at the TOC visit in the clinically modified intent-to-treat (cMITT) population.
Secondary:	**Secondary:**	**Secondary:**
• To estimate clinical response to CAZ-AVI in HAP patients, and HAP patients with demonstrated Gram-negative pathogens.	• Using a composite estimand strategy to estimate the clinical response rate at the end of treatment (EOT) visit in participants who meet minimum disease requirements, and at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens (excluding participants not expected to respond to CAZ-AVI for both target populations). Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before EOT visit (or TOC visit accordingly) where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering further antibiotics treatment will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and EOT visit (or TOC visit accordingly) inclusive, development of infectious complications of pneumonia after Day 2 triggering further antibiotics treatment will be regarded as failure clinical response.	• The proportion of participants with clinical cure at the EOT visit in cMITT population, and at the EOT, TOC visits in the microbiologically modified intent-to-treat (mMITT) population.
• To estimate the microbiologic response to CAZ-AVI.	• Using a composite estimand strategy to estimate the per-patient and per-pathogen microbiological response rate at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens. Microbiological response will be categorized as favorable (ie, eradication, or presumed eradication), unfavorable (persistence, persistence with increasing minimum inhibitory concentration [MIC], or presumed persistence), and indeterminate. Per-pathogen microbiological response will be summarized with the proportion of participants achieving favorable response by baseline pathogen type; per-patient microbiological response will be summarized with the proportion of participants achieving overall favorable response (ie,	• The proportion of participants with the favorable per-patient microbiologic response at the EOT and TOC visits in the mMITT population. • The proportion of favorable per-pathogen microbiologic responses at the EOT and TOC visits in the mMITT population.

Objectives	Estimands	Endpoints
	favorable for each of the baseline pathogen isolate). Intercurrent events of death or identification of an infectious complication of pneumonia triggering further antibiotics treatment such that an adequate source specimen is not available to culture will be regarded as an indeterminate microbiological response if clinical response is indeterminate, and will be regarded as a presumed eradication if a clinical cure is assessed.	
• To estimate the efficacy of CAZ-AVI in patients with pathogens resistant to ceftazidime.	• Using the same composite estimand strategies as the primary estimand and aforementioned secondary estimands to estimate the proportions of participants with clinical cure and with a favorable per-patient microbiological response at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens that are resistant to ceftazidime.	• The proportion of participants with clinical cure, and proportion of participants with favorable per-patient microbiologic response at the EOT and TOC visits in patients with pathogens resistant to ceftazidime in the mMITT population.
• To estimate all-cause mortality for CAZ-AVI.	• Using a treatment-policy estimand strategy in participants who meet minimum disease requirements, and in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens to estimate the proportion of participants with death at the TOC visit and Day 28 of the study. Any death that occurred after the first dose of study intervention through the nominal analysis timepoint will be included. A participant with the last known survival status that is before the nominal analysis timepoint or missing at the nominal analysis timepoint will be reported as an unknown status.	• The proportion of participants with death due to any cause (all-cause mortality) at the TOC visit and at Day 28 in the cMITT and mMITT populations.
• To evaluate the safety and tolerability of CAZ-AVI.	• N/A.	• Assessment of treatment-emergent adverse events (TEAEs) and safety-related clinical laboratory tests and vital observations.

Overall Design

This is a prospective, single arm, open-label, multi-center clinical study evaluating the effectiveness and safety of CAZ-AVI in participants with HAP (including VAP), who have initiated treatment with CAZ-AVI in an inpatient hospital setting. The duration of antibiotic treatment with the study intervention is 7-14 days. Participants must receive intravenously (IV) study intervention in the hospital for at least 7 full days.

Number of Participants

Approximately 235 participants will be enrolled to study intervention such that approximately 200 participants will be evaluable for clinical cure rate in the cMITT population.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Each participant is expected to complete the study, including follow-up, within approximately 6 weeks. The duration of antibiotic treatment with study intervention is 7-14 days. Participants must receive IV study intervention for at least 7 days. At any time after 7 days, the investigator will have the option to continue IV study intervention or discontinue study intervention completely. Total therapy should not exceed 14 days.

Participants will receive CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) administered IV as 2 hours infusion every 8 hours (q8h). Dose adjustments for participants with creatinine clearance (CrCL) ≤50 mL/min will be applied based on the approved label (Section 6.1.1).

In addition, participants for whom baseline cultures are still pending at registration will receive empiric linezolid or vancomycin to cover for Gram-positive pathogens for 48 to 72 hours after Day 1; continuation or discontinuation of Gram-positive coverage after this period will be dependent on the final culture results (Section 6.1.1.1).

Certain participants will receive empiric Gram-negative antibiotic coverage with amikacin for 48 to 72 hours after enrollment to cover for multi-drug resistant Gram-negative organisms while awaiting susceptibility results (Section 6.1.1.2).

For participants who discontinue study intevention early, all subsequent scheduled assessments should be collected. The EOT visit should occur within 24 hours of study intervention discontinuation.

A participant may withdraw from the study at any time at his/her own request. The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. The participant will be permanently discontinued both from the study intervention and from the study at that time.

Data Monitoring Committee or Other Independent Oversight Committee:

None.

Statistical Methods

In general, categorical variables (such as clinical response, microbiological response, mortality, etc) will be summarized by number of participants (n), and proportion of participants in each category. In particular, clinical response rate and microbiological response (patient-level) rates will be presented with corresponding 2-sided 95% confidence intervals (CI).

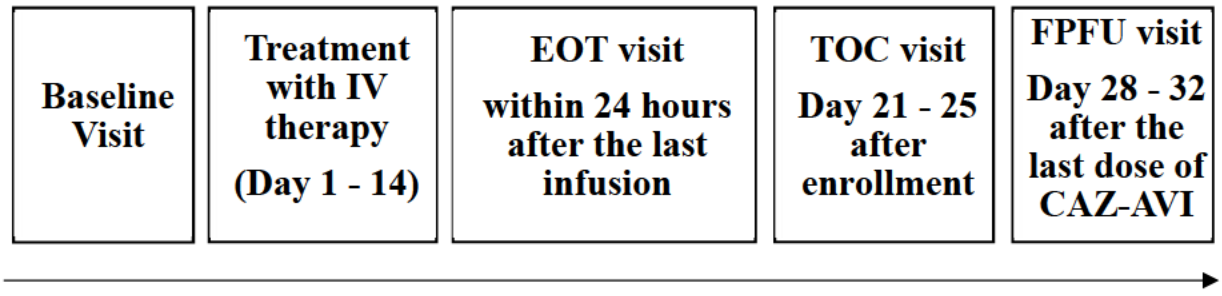
Results will be presented side-by-side with the global results observed in the REPROVE study. Subgroup analyses will be performed and be compared with same subgroups in the REPROVE study. The comparisons of results between this study and REPROVE study will not be subject to statistical comparison due to different study times, operations, drug resistance, etc.

Safety data will be presented in tabular and/or graphical format and summarized descriptively. All TEAEs, relationship with treatment, discontinuations due to adverse events (AEs), laboratory data abnormality will be summarized with frequency and percentages. Change from baseline for selected laboratory tests and vital signs will be summarized with descriptive statistics.

Further details will be included in a Statistical Analysis Plan (SAP) including analysis sets, definition of clinical cure rate and microbiological response, and methodology for analyzing efficacy and safety data.

1.2. Schema

Figure 1. Study Outline



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier Abbreviations used in this table may be found in Appendix 8	**Screening**	**Treatment Period[a]**		**End of Treatment**	**Test of Cure**	**Final Protocol Follow Up**
Visit Window	**Visit 1 Day -1[c]**	**Visit 2[b] Day 1**	**Visits 3 - 15 Day 2 - 14 after enrollment**	**Visit 16 within 24 hours after the completion of the last infusion of study intervention**	**Visit 17 Day 21 - 25 after enrollment**	**Visit 18 28 - 32 days after last dose of CAZ-AVI**
ELIGIBILITY						
Informed consent	X					
Confirm eligibility criteria	X	X				
Demographics	X					
Medical history	X					
Review prior medications (including prior antibiotic therapy)[d]	X	X				
Ventilator device status	X	X	X (daily)	X	X	
PHYSICAL EXAMINATION						
Body weight and height	X					
Complete physical examination[e]	X			X	X	
Vital signs[f]	X	X	X (daily)	X	X	
Disease characteristics						
Chest X-ray or CT scan	X[g]			X	X	
Arterial blood gas[h]	X					
APACHE II score (See Appendix 6)[i]	X					
Blood cultures (local and central lab)[j]	X[k]	----------As clinically indicated----------				

Visit Identifier Abbreviations used in this table may be found in Appendix 8	**Screening**	**Treatment Period**[a]		**End of Treatment**	**Test of Cure**	**Final Protocol Follow Up**
Visit Window	**Visit 1 Day -1**[c]	**Visit 2**[b] **Day 1**	**Visits 3 - 15 Day 2 - 14 after enrollment**	**Visit 16 within 24 hours after the completion of the last infusion of study intervention**	**Visit 17 Day 21 - 25 after enrollment**	**Visit 18 28 - 32 days after last dose of CAZ-AVI**
Appropriate respiratory specimen for Gram stain/culture (local and central lab)	X[l]	X[m]		X[n]	X	
LABORATORY (local lab)[o]						
Hematology	X	X	Day2. Then every 3 days	X	X	
Blood chemistry	X	X	Day2. Then every 3 days[p]	X	X	
Urinalysis	X					
Coagulation	X	X	Day2. Then every 3 days	X	X	
Pregnancy test[q]	X	X				
Contraception check	X	X			X	X
Estimate creatinine clearance[r]	X	X (as clinically indicate)	Day 2. Then every 3 days (and as clinically indicated)[s]	X	X	
REGISTRATION		X				
STUDY INTERVENTION						
Study intervention administration		X	X (daily)			
Stop empiric antibiotics			X[t]			
ASSESSMENTS						
Clinical signs and symptoms	X	X	X (daily)	X	X	
Clinical response				X	X	
SERIOUS AND NON-SERIOUS AE MONITORING	X	→	→	→	→	→
Mortality		X	X (daily)	X	X	X

Visit Identifier Abbreviations used in this table may be found in Appendix 8	Screening	Treatment Period[a]		End of Treatment	Test of Cure	Final Protocol Follow Up
Visit Window	**Visit 1 Day -1[c]**	**Visit 2[b] Day 1**	**Visits 3 - 15 Day 2 - 14 after enrollment**	**Visit 16 within 24 hours after the completion of the last infusion of study intervention**	**Visit 17 Day 21 - 25 after enrollment**	**Visit 18 28 - 32 days after last dose of CAZ-AVI**
CONCOMITANT TREATMENT(S)[u]		X	→	→	→	X

a. minimum of 7 full days (21 doses for participants with normal renal function and participants with mild renal impairment) to a maximum of 14 days, where a full day is defined as a 24-hour period.

b. Visit 2 includes the baseline visit and the first 24 hours therapy. All procedures at Visit 2 are to be done before the 1st dose of the study intervention. Administration of the first dose of IV study intervention marks the beginning of study treatment Day 1. Subsequent study treatment days are based on 24 hours periods from the time of the first infusion.

c. Study treatment should be started as soon as a participant's eligibility has been confirmed and the participant has been enrolled. Consequently, Day −1 may be the same calendar day as Day 1.

d. All medications from signed informed consent to Day 1 should be recorded. Systemic antibiotics should be documented from 2 weeks prior to study entry.

e. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. If the participant's actual height and weight are not available, the height and weight may be estimated for study use. All height and weight measurements should be recorded in the CRF as actual or estimated. After screening visit, weight should be measured as clinically indicated.

f. Tympanic or axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 1 blood pressure measurements.

g. Chest X-ray or CT scan obtained within 48 hours prior to screening may be used.

h. Required for ventilated participants; recommended for non-ventilated participants.

i. Calculate APACHE using most recent local laboratory results. Use of temperature obtained rectally in determining the APACHE II score is preferred but not mandatory. See Appendix 6. If an arterial blood gas is not clinically indicated, the APACHE score should be calculated using serum bicarbonate and oxygenation should be presumed normal.

j. All participants require 2 sets of blood cultures (1 anaerobic and 1 aerobic bottle in each set) at within 24 hours prior to Day 1. If participants are bacteremic, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. If repeat cultures have not been finalized negative by the time of the EOT visit, a set of repeat blood cultures should be obtained at the EOT visit. Blood cultures should also be obtained as clinically indicated. See Section 8.1.2.1 for details of sample collection.

k. Blood culture samples obtained in the 24 hours prior to Day 1 are acceptable.

l. Respiratory cultures from 48 hours prior to Day 1 may be used, but participants ventilated at the time of enrollment, regardless of whether they meet the criteria for VAP, must have a specimen obtained while ventilated.

Visit Identifier Abbreviations used in this table may be found in Appendix 8	Screening	Treatment Period[a]		End of Treatment	Test of Cure	Final Protocol Follow Up
Visit Window	**Visit 1 Day -1[c]**	**Visit 2[b] Day 1**	**Visits 3 - 15 Day 2 - 14 after enrollment**	**Visit 16 within 24 hours after the completion of the last infusion of study intervention**	**Visit 17 Day 21 - 25 after enrollment**	**Visit 18 28 - 32 days after last dose of CAZ-AVI**

m. Repeat respiratory cultures are not required unless a screening sample was obtained from a non-ventilated participant and the participant is ventilated between screening and baseline (or participants who had a bronchoscopy performed between screening and baseline). In this case an appropriate respiratory specimen should be obtained via BAL, miniBAL, PBS sample or endotracheal aspirate at the baseline visit.

n. If treatment is discontinued early because the participant is failing therapy or other reasons, an appropriate respiratory specimen for culture should be obtained, ideally after stopping the initial treatment but before the new treatment is administered.

o. Refer to Appendix 2 for details on collection of the required laboratory variables. If Day 1 and Screening Visit occur on the same calendar day, lab results from Screening Visit can be used on Day 1 visit.

p. When amikacin is co-administered, the serum creatinine should be measured on Day 2, then every 3 days, then based on clinical judgment and in line with amikacin prescribing information during the study treatment period. The dose should be adjusted appropriately.

q. Pregnancy tests may be urine or serum tests. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second pregnancy test will be required at the baseline visit prior the participant's receiving the CAZ-AVI.

r. Estimate creatinine clearance using the Cockcroft-Gault method (see Appendix 7).

s. Day 2. Then every 3 days and as clinically indicated. When appropriate, adjust study intervention dosage as per Section 6.1. However, when amikacin is co-administered, the CrCL should be measured in line with amikacin labeling and dose of amikacin adjusted appropriately.

t. At 48 hours (or at 72 hours if results are not available at 48 hours), empiric Gram–positive linezolid (or vancomycin) should be stopped depending on pathogen identification as outlined in Section 6.1.1.1 and Figure 2; and empiric Gram-negative amikacin should be stopped depending on pathogen identification and susceptibility results as outlined in Section 6.1.1.2 and Figure 3.

u. Collection of concomitant treatments will include blood and other blood product transfusions.

2. INTRODUCTION

Ceftazidime-avibactam (CAZ-AVI) is a β-lactam/β-lactamase inhibitor developed as an IV administered compound for parenteral treatment of participants with infections caused by Gram-negative pathogens, including pathogens that are resistant to ceftazidime.

Hospital-Acquired Pneumonia
HAP is defined as pneumonia that occurs 48 hours or more after admission, without being in the incubation period of infection at the time of admission. VAP is a sub-type of HAP and is defined as pneumonia that occurs 48 hours or more after mechanical ventilation in patients undergoing endotracheal intubation or tracheotomy[1]. In the US, the incidence of hospital-acquired infections in hospitalized patients was 4%, of which pneumonia accounted for approximately 21.8%[2]. According to the results of a cross-sectional survey of large-scale nosocomial infection in China, the incidence of hospital-acquired infections in hospitalized patients was approximately 3%-5%, among which, the incidence of hospital-acquired lower respiratory tract infection was approximately 2%[3, 4].

Antibiotic resistance of HAP in China
The most common resistant Gram-negative pathogens causing HAP/VAP in China include extended spectrum β-lactamase-producing Enterobacteriaceae, CRE, CRAB and CRPA[1]. Data from China multicenter bacterial resistance networks (ie, China surveillance network for bacterial resistance [CHINET], 2004-2015[5], and Chinese antimicrobial resistance surveillance of nosocomial infection [CARES], 2016[6]) showed that the isolation rate of ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli* was 25% ~ 35% and 45% ~ 60% respectively, and the rate of CRE was 5% ~ 18% among various specimens (eg, blood, urine, sputum).

Ceftazidime-Avibactam
CAZ-AVI comprises ceftazidime, an established injectable third generation cephalosporin antimicrobial agent, and avibactam, a novel non-β-lactam β lactamase inhibitor with a spectrum including Ambler Class A ESBLs, Class A serine carbapenemases (eg, KPC), Class C (AmpC) enzymes, and some Class D (OXA) β-lactamase enzymes. It is not active against class B metallo-β-lactamases, and it is not active against *Acinetobacter baumannii*. CAZ-AVI has been developed as an IV administered compound for treatment of patients with infections caused by Gram-negative pathogens, including pathogens that are resistant to ceftazidime (CAZ-resistant). CAZ-AVI was approved by the Food and Drug Administration (FDA) in the US on 25 February 2015, and was approved in the European Union (EU) on 24 June 2016. In China, CAZ-AVI was approved by the NMPA on 21 May 2019. Indications for adults approved include cIAI, HAP (including VAP), and for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.

2.1. Study Rationale

China has participated in 2 international Phase 3 clinical trials for CAZ-AVI that have been completed, including 1 study in patients with HAP (including VAP), which demonstrated the non-inferiority (NI) of CAZ-AVI to meropenem for the treatment of HAP/VAP, including

infections due to Gram-negative pathogens resistant to ceftazidime. No new safety concerns were identified.

The purpose of the study is to further evaluate effectiveness of CAZ-AVI in Chinese participants with HAP, including VAP. CCI [redacted].

2.2. Background

In the face of increasing global antibiotic resistance, there are limited therapeutic options for the treatment of resistant Gram-negative pathogens. There is an urgent need for new antibiotics to treat serious infections caused by Gram-negative bacteria proven or suspected to be caused by β-lactam resistant pathogens, including those producing ESBLs and KPCs.

A new therapeutic agent that is able to demonstrate similar efficacy and safety to the current carbapenem standard of care, including efficacy in patients with Enterobacteriaceae and P. aeruginosa infections and activity against key β-lactam resistant pathogens is an important, clinically significant addition to the currently limited armamentarium that is available to physicians.

The addition of avibactam to ceftazidime expands its antibacterial activity against pathogens possessing β-lactamases that are susceptible to inhibition by avibactam, while retaining the bactericidal activity of ceftazidime[7]; it therefore has the potential to restore the utility of ceftazidime in the clinical setting. Efficacy and safety has been demonstrated in clinical trials, including in infections caused by CAZ-resistant, but CAZ-AVI-susceptible pathogens.

In China, CAZ-AVI was approved by the NMPA on 21 May 2019.

2.2.1. Clinical Overview

There are 18 completed Phase 1 clinical pharmacology studies, including:

- 13 studies with administration of avibactam alone and/or CAZ-AVI by IV infusion (including 1 study conducted in pediatric participants)
- Avibactam PK data from 5 Phase 1 clinical pharmacology studies in the ceftaroline-avibactam (CXL) development program, as it has been demonstrated that there is no PK interaction between CXL and avibactam.

There are also 2 completed Phase 2 studies in adults (1 in complicated urinary tract infection [cUTI] and 1 cIAI) and 5 Phase 3 clinical studies:

- RECLAIM, a double-blind study in adult participants with cIAI.
- RECLAIM3, a double-blind study in adult Asian participants with cIAI.
- REPRISE, an open-label study in adult participants with cUTI or cIAI, who had ceftazidime-resistant pathogens at baseline.

- RECAPTURE, a double-blind study in adult participants with cUTI.
- REPROVE, a double-blind study in adult participants with HAP, including VAP.

Across the CAZ-AVI Phase 3 studies in participants with cIAI, cUTI and HAP, CAZ-AVI (±metronidazole [MTZ]) at the proposed dose was effective in participants with both CAZ-susceptible and CAZ-resistant pathogens. The observed safety profile supports the use of CAZ-AVI in the approved indications in Chinese adults.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of CAZ-AVI may be found in the China local product document (LPD), which is the single reference safety document (SRSD) for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) CAZ-AVI		
Potential risks associated with CAZ-AVI include the following: • Encephalopathy and neurological symptoms such as tremor, coma and seizures in patients with renal impairment who do not have their dose appropriately reduced	The potential risks are based on product labeling for CAZ-AVI. This potential risk has been reported with ceftazidime when the dose has not been reduced in patients with renal impairment.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). The dose should be reduced according to the degree of renal impairment (see Section 6.1). In participants with renal impairment, close monitoring of estimated creatinine clearance is advised.
Study Procedures ***(Not applicable)***		
Other ***(Not applicable)***		

2.3.2. Benefit Assessment

Participants enrolled into this clinical study will have required hospitalization due to other illnesses and will have developed HAP that requires treatment with IV antibiotics. The potential benefit to participants in this study is that they will receive effective antibiotic therapy for their infection based on clinical practice. The potential benefit of the study, in general, is to further characterize the efficacy and safety of a novel antibiotic product in a large sample size in Chinese after marketing approval, that is an effective treatment for HAP/VAP in the face of the changing pattern of antibiotic resistance.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with CAZ-AVI are justified by the anticipated benefits that may be afforded to participants with HAP, including VAP.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To estimate clinical response to CAZ-AVI in HAP patients.	• Using a composite estimand strategy to estimate the clinical response rate at the TOC visit in participants who meet minimum disease requirements (excluding participants not expected to respond to CAZ-AVI). Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before TOC visit where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering treatment with further antibiotics will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and TOC visit inclusive, development of infectious complications of pneumonia after Day 2 until TOC visit triggering treatment with further antibiotics will be regarded as failure clinical response.	• The proportion of participants with clinical cure at the TOC visit in the cMITT population.
Secondary:	**Secondary:**	**Secondary:**
• To estimate clinical response to CAZ-AVI in HAP patients, and HAP patients with demonstrated Gram-negative pathogens.	• Using a composite estimand strategy to estimate the clinical response rate at the EOT visit in participants who meet minimum disease requirements, and at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens (excluding participants not expected to respond to CAZ-AVI for both target populations). Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before EOT visit (or TOC visit accordingly) where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering further antibiotics treatment will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and EOT visit (or TOC visit accordingly) inclusive, development of infectious complications of pneumonia after Day 2 triggering further antibiotics treatment will be regarded as failure clinical response.	• The proportion of participants with clinical cure at the EOT visit in cMITT population, and at the EOT, TOC visits in the mMITT population.

Objectives	Estimands	Endpoints
• To estimate the microbiologic response to CAZ-AVI.	• Using a composite estimand strategy to estimate the per-patient and per-pathogen microbiological response rate at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens. Microbiological response will be categorized as favorable (ie, eradication, or presumed eradication), unfavorable (persistence, persistence with increasing MIC, or presumed persistence), and indeterminate. Per-pathogen microbiological response will be summarized with the proportion of participants achieving favorable response by baseline pathogen type; per-patient microbiological response will be summarized with the proportion of participants achieving overall favorable response (ie, favorable for each of the baseline pathogen isolate). Intercurrent events of death or identification of an infectious complication of pneumonia triggering further antibiotics treatment such that an adequate source specimen is not available to culture will be regarded as an indeterminate microbiological response if clinical response is indeterminate, and will be regarded as a presumed eradication if a clinical cure is assessed.	• The proportion of participants with the favorable per-patient microbiologic response at the EOT and TOC visits in the mMITT population. • The proportion of favorable per-pathogen microbiologic responses at the EOT and TOC visits in the mMITT population.
• To estimate the efficacy of CAZ-AVI in patients with pathogens resistant to ceftazidime.	• Using the same composite estimand strategies as the primary estimand and aforementioned secondary estimands to estimate the proportion of participants with clinical cure and with a favorable per-patient microbiological response at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens that are resistant to ceftazidime.	• The proportion of participants with clinical cure, and proportion of participants with favorable per-patient microbiologic response at the EOT and TOC visits in patients with pathogens resistant to ceftazidime in the mMITT population.
• To estimate all-cause mortality for CAZ-AVI.	• Using a treatment-policy estimand strategy in participants who meet minimum disease requirements, and in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens to estimate the proportion of participants with death at the TOC visit and Day 28 of the study. Any death that occurred after the first dose of study intervention through the nominal analysis timepoint will be included. A participant with the last known survival status that is before the nominal analysis timepoint or missing at the nominal analysis timepoint will be reported as an unknown status.	• The proportion of participants with death due to any cause (all-cause mortality) at the TOC visit and at Day 28 in the cMITT and mMITT populations.
• To evaluate the safety and tolerability of CAZ-AVI.	• N/A.	• Assessment of TEAEs and safety-related clinical laboratory tests and vital observations.

4. STUDY DESIGN

4.1. Overall Design

This is a single arm, multi-center interventional study evaluating the effectiveness and safety of CAZ-AVI in Chinese adults with HAP (including VAP).

Approximately 235 participants will be enrolled. Each participant is expected to complete the study, including follow-up, within approximately 6 weeks. The study intervention will be administered IV for a minimum of 7 days and a maximum of 14 days. Participants must receive the study intervention for at least 7 days. At any time after 7 days, the investigator will have the option to continue the study intervention or discontinue the study intervention completely.

The participant is to return to the study center for the scheduled visits following discharge from the hospital. An overall clinical assessment, vital sign measurements, ventilation status and detailed pulmonary assessment will be performed at Day 1 (baseline), daily during treatment with IV therapy, and at the EOT, and TOC (21 to 25 calendar days from enrollment) visits. In addition to these visits, death and AEs will be assessed until the final protocol follow up (FPFU) visit (28 to 32 calendar days after the last dose of CAZ-AVI). The FPFU visit may be conducted either in person or by telephone contact (Figure 1).

Note: The investigors must continue to collect AEs and perform safety reporting responsibilities per protocol via telephone contact or other methods as appropriate if on-site vists interrupted by the COVID-19 pandemic.

4.2. Scientific Rationale for Study Design

This study is designed CCI [redacted] to further evaluate effectiveness of CAZ-AVI in Chinese patients with HAP, including VAP. The NI of CAZ-AVI compared with meropenem was demonstrated in overall population in co-primary endpoints (clinical cure rate at TOC visit in clinically modified intent-to-treat [cMITT] and clinical evaluable [CE] population) in REPROVE study. Comparative data in Chinese subgroup showing a consistent trend are also available in REPROVE study. To utilize more of the possible participants and estimate/evaluate the efficacy of CAZ-AVI in a relative large sample size after the marketing approval, a descriptive estimation study is planned in China as CCI [redacted].

Empiric agents have been selected to cover Gram-positive pathogens and multi-drug resistant Gram-negative pathogens which may exhibit resistance to CAZ-AVI. Empiric agents are defined as those antimicrobials administered to the participant prior to knowledge of the respiratory specimen culture and susceptibility results. CAZ-AVI may not adequately cover certain species of Gram-positive and Gram-negative organisms that can cause HAP. Because prompt delivery of antibiotic with activity against the etiologic agent has been shown to decrease morbidity and mortality among participants with HAP and because culture and susceptibility results are not known until approximately 48 to 72 hours after they are obtained, use of empiric coverage with agents that cover both resistant Gram-negative and Gram-positive organisms is standard clinical practice in many regions around the world. In

this study, empiric Gram-positive and Gram-negative agents will be used for all participants whose culture results are not available at the time of recruitment. After 48-72 hours, the criteria for discontinuing empiric antibiotics are outlined in Sections 6.1.1.1and 6.1.1.2.

Human reproductive safety data are limited for CAZ-AVI, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

The intention for CAZ-AVI is that it will be active in participants with HAP or VAP caused by Gram-negative bacteria that express various non-metallo-β-lactamases. The dosing regimen for this study will be based on the approved dose recommended for treatment of HAP/VAP in the package insert, which was established following: (i) acquisition of preclinical data, including surveillance of minimum inhibitory concentrations (MICs) among Gram-negative bacteria isolated from nosocomial pneumonia participants and results from mouse infection models; (ii) measurements of penetration into epithelial lining fluid; and (iii) completion of the Phase 2 and Phase 3 clinical studies in participants with cIAI, cUTI or HAP.

For patients with changing renal function, doses of CAZ-AVI will be modified as needed in accordance with the approved package insert.

The doses of linezolid, vancomycin and amikacin should follow the local package insert.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants ≥18 and ≤90 years of age at Visit 1 (Screen 1).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Onset of signs and symptoms (including Inclusion Criteria 4, 6, and 7) ≥48 hours after admission or <7 days after discharge from an inpatient acute or chronic care facility.

4. New or worsening infiltrate on chest X-ray or CT scan obtained within 48 hours prior to screening.

5. Respiratory specimen obtained for Gram stain and culture within 48 hours prior to screening, and after the onset of signs and symptoms of HAP (ideally before receipt of any systemic antibiotics).

6. At least 1 of the following systemic signs:

    - Fever (temperature >38°C) or hypothermia (rectal/core temperature <35°C)

    - White blood cell (WBC) count >10,000 cells/mm^3, or WBC count <4500 cells/mm^3, or >15% band forms.

7. At least 2 of the following respiratory signs or symptoms:

    - A new onset of cough (or worsening of cough).

    - Production of purulent sputum or endotracheal secretions.

    - Auscultatory findings consistent with pneumonia/pulmonary consolidation (eg, rales, rhonchi, bronchial breath sounds, dullness to percussion, egophony).

    - Dyspnea, tachypnea or hypoxemia (O_2 saturation <90% or PaO_2 <60 mmHg while breathing room air).

- A need for mechanical ventilation or, for already ventilated participants, acute changes made in the ventilator support system to enhance oxygenation, as determined by, for example arterial blood gas or worsening PaO_2/FiO_2.

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Participant has a past or current history of known or suspected *Clostridium difficile* associated diarrhea (CDAD).

3. Pulmonary disease that precludes evaluation of therapeutic response (including, but not limited to, lung cancer, active tuberculosis, cystic fibrosis, granulomatous disease, fungal pulmonary infection or recent pulmonary embolism)

4. Participants with lung abscess, pleural empyema or post obstructive pneumonia.

5. Participants receiving hemofiltration or peritoneal dialysis.

6. Any allergy to cephalosporins regardless of seriousness of that reaction. Severe hypersensitivity to any other betalactams (eg, penicillins, monobactams or carbapenems).

7. Participant is expected to require a treatment course for HAP longer than 14 days.

Prior/Concomitant Therapy:

8. Co-administration of CAZ-AVI with probenecid or chloramphenicol and co-administration of any systemic antibiotic other than per protocol is not allowed.

9. The total duration of antibiotic exposure for antibiotics whose administration begins in the 48 hours prior enrollment is longer than 24 hours (eg, administration of more than 3 doses of a q8h antibiotic or more than 1 dose of a q24h antibiotic).

- However, participants are still eligible for entry if ALL pathogens identified at baseline are resistant to ALL of the antibiotics received; or the total duration of antibiotic exposure* of the antibiotics for which ANY of the pathogens identified at baseline were found to be susceptible, in the ≤48 hours, is ≤24 hours.

- AND the participant has shown objective signs of worsening despite therapy as demonstrated by at least 1 of the below:

    - Increased oxygen requirement

    - Two of the following: increased dyspnea, increased purulent sputum, increased tachypnea, increased WBC count.

* This excludes antibiotics that are not systemically absorbed (eg, topical antibiotics, oral vancomycin).

Prior/Concurrent Clinical Study Experience:

10. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

11. Acute Physiology and Chronic Health Evaluation (APACHE) II score >30 or <10 using the available data within 24 hours prior baseline.

12. When culture results from a 48 hours specimen period prior to screening are available [Note: This can be from any culture and not just the baseline culture], and any of the following is present:

    - The participant is found to have HAP caused by Gram-positive organisms without concomitant infection with a Gram-negative pathogen (polymicrobial infections with Gram-positive pathogens are permitted as long as a Gram-negative pathogen is also present).

    - The participant is found to have HAP caused by a Gram-negative species not expected to respond to CAZ-AVI (eg, Acinetobacter baumanii, Stenotrophomonas spp). Note: the participant is allowed to participate in the study if the investigator considers that the species is a colonizer which does not warrant specific treatment and other criteria are met.

    - The participant is found to have HAP caused by a Gram-negative pathogen demonstrating resistance to carbapenems and/or CAZ-AVI.

Other Exclusions:

13. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Controlled sodium diet

Each vial contains a total of 6.44 mmol of sodium (approximately 148 mg), which is equivalent to 7.4% of the maximum daily sodium intake recommended by World Health Organization (WHO). The maximum daily dose of this product is equivalent to 22.2% of the maximum daily sodium intake recommended by the WHO. This should be considered when administering CAZ-AVI to participants who are on a controlled sodium diet.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). The pariticipants who are screen failures will not be re-screened.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

Not Applicable.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to CAZ-AVI.

6.1. Study Intervention(s) Administered

Intervention Name	Zavicefta (ceftazidime/avibactam or CAZ-AVI)
Type	Drug
Dose Formulation	Powder for solution for injections
Unit Dose Strength(s)	CAZ-AVI 2.5g: ceftazidime 2g + avibactam 0.5g
Dosage Level(s)	CAZ-AVI 2.5 g administered IV as 2 hours infusion every 8 hours (q8h). Refer to Table 1 for participants with estimated CrCL ≤50 mL/min
Route of Administration	Infusion
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor *Refer to IP manual*
Packaging and Labeling	Study intervention will be provided in a sealed vial within a carton containing 1 vial per carton and is labeled in a way that is consistent with the study design and with the regulatory requirement in China. *Refer to IP manual*

Table 1. Recommended IV Doses for Participants With Estimated CrCL ≤50 mL/min[1]

Estimated CrCL (mL/min)	Dose regimen[2]	Frequency[4]	Infusion time
31~50	1.25 g（1 g/0.25 g）	Every 8 hours	2 hours
16~30	0.94 g（0.75 g/0.19 g）	Every 12 hours	2 hours
6~15	0.94 g（0.75 g/0.19 g）	Every 24 hours	2 hours
≤5[3]	0.94 g（0.75 g/0.19 g）	Every 48 hours	2 hours

1. CrCL estimated using the Cockcroft-Gault formula.
2. Dose recommendations are based on pharmacokinetic modelling.
3. Ceftazidime and avibactam are removed by haemodialysis. Dosing of CAZ-AVI on haemodialysis days should occur after completion of haemodialysis.
4. Time windows of dose frequency are Q8H ± 30mins, Q12H ± 30mins, Q24H ± 30mins and time window of infusion time is 2 hours ± 10mins.

6.1.1. Administration

Participants will receive CAZ-AVI (2000 mg of ceftazidime and 500 mg of avibactam) administered by IV infusion in a volume of 100 mL at a constant rate over 2 hours.

For participants with estimated CrCL ≤50 mL/min, please refer to Table 1.

The duration of antibiotic treatment with study intervention is 7-14 days. Participants must receive IV study intervention in the hospital for at least 7 days. At any time after 7 days, the investigator will have the option to continue IV study intervention or discontinue study intervention completely. Total therapy should not exceed 14 days.

When protocol defined empiric antibiotics provided by Pfizer are scheduled to be delivered at the same time as study intervention after the first dose, they may be given after the delivery of study intervention or concurrently via an alternative IV line or lumen. See Sections 6.1.1.1 and 6.1.1.2 for specific details regarding the administration of the empiric Gram-positive and Gram-negative agents.

6.1.1.1. Empiric Gram-positive agent

Linezolid should be given to all participants in whom baseline cultures are still pending at registration as empiric Gram-positive coverage for 48 hours (unless culture results are not available at 48 hours post-registration in which case, use may be extended for an additional 24 hours [to a maximum of 72 hours post-registration]). Under certain circumstances, there may be reasons why a specific participant cannot or should not receive linezolid and in this instance vancomycin should be used instead.

In the following circumstances, individual participants must receive vancomycin instead of linezolid (ie, there is a contraindication to linezolid):

- Hypersensitivity to linezolid or any of its known components
- Participant has taken a monoamine oxidase inhibitor within 2 weeks prior to enrollment
- Participant has uncontrolled hypertension, pheochromocytoma, thyrotoxicosis or carcinoid syndrome
- Participant is taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (eg, pseudoephedrine), vasopressive agents (eg, epinephrine, norepinephrine), dopaminergic agents (eg, dopamine, dobutamine)
- Participant is taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone

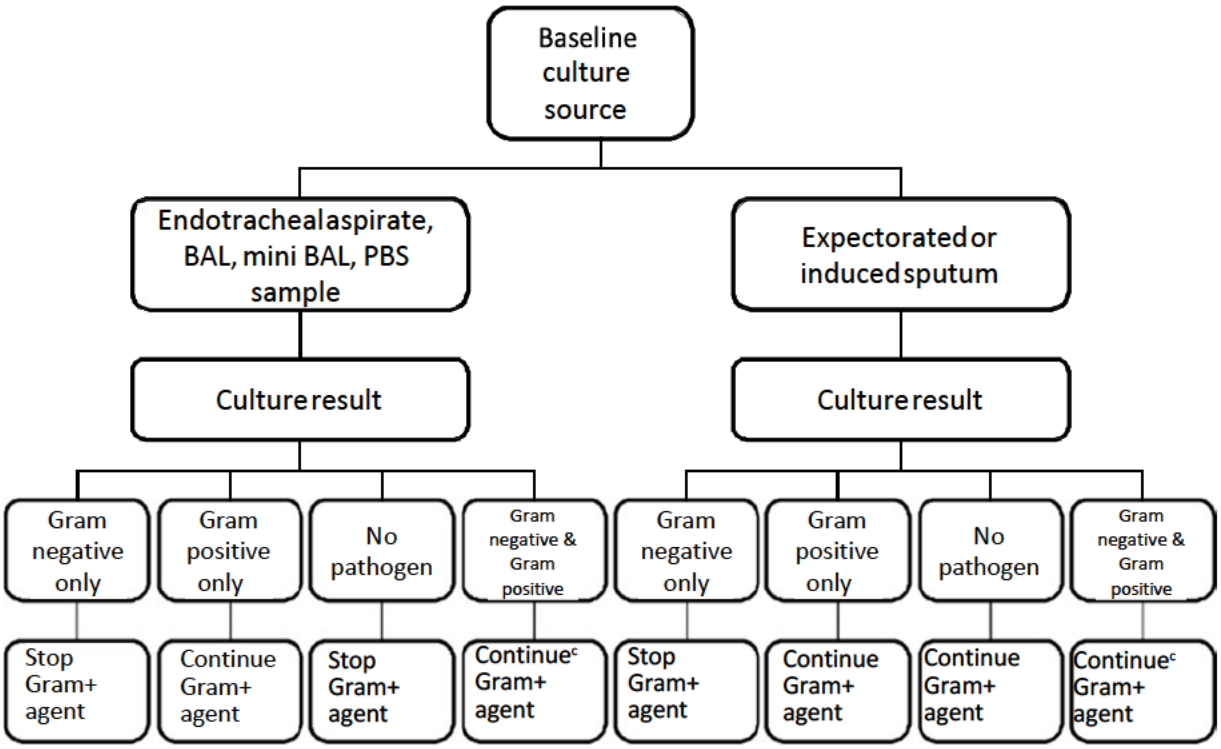
In the following circumstances, individual participants may, at the investigator's discretion, receive vancomycin instead of linezolid:

- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia)
- Participant is receiving insulin or oral hypoglycaemic agents for diabetes mellitus

Dosing for linezolid and vancomycin refer to package insert. Participants should receive Gram-positive agents for 48 hours. At 48 hours, the Gram-positive agent should be continued or stopped based on the etiologic pathogens identified in the baseline culture as described in Figure 2. If the etiologic pathogen has not been identified at 48 hours, therapy may be continued for an additional 24 hours (ie, 72 hours total of empiric Gram-positive therapy).

For participants in whom Gram-positive agent continuation is indicated after pathogen identification, the duration of therapy should be consistent with study intervention; duration must not be longer than 14 days. Study intervention should continue for 7-14 days, regardless of the need for ongoing Gram-positive therapy.

Figure 2. Algorithm for Stopping or Continuing Open-label Empiric Gram-positive Agent Based on Baseline Culture Results at 48 Hours[a,b]



a. For details regarding use of study intervention, see Section 6.1.1.

b. If cultures results are not available at 48 hours, empiric Gram-positive agents may be continued for an additional 24 hours (ie 72 hours of total therapy).

c. If the investigator considers the Gram-positive organisms to be a colonizer which does not warrant treatment, empiric Gram-positive treatment may be stopped.

6.1.1.2. Empiric Gram-negative agent

Amikacin is the agent for empiric Gram-negative double coverage.

All participants should receive amikacin for 48 hours if susceptibility results from the baseline culture are not available prior to registration (a maximum of 72 hours if susceptibility results are still not available at 48 hours post-registration) except in instances where an individual participant has a contraindication to aminoglycoside use (namely, myasthenia gravis), or is at low risk of infection with multi-drug resistant Gram-negative organisms as defined by the absence of all of the following criteria:

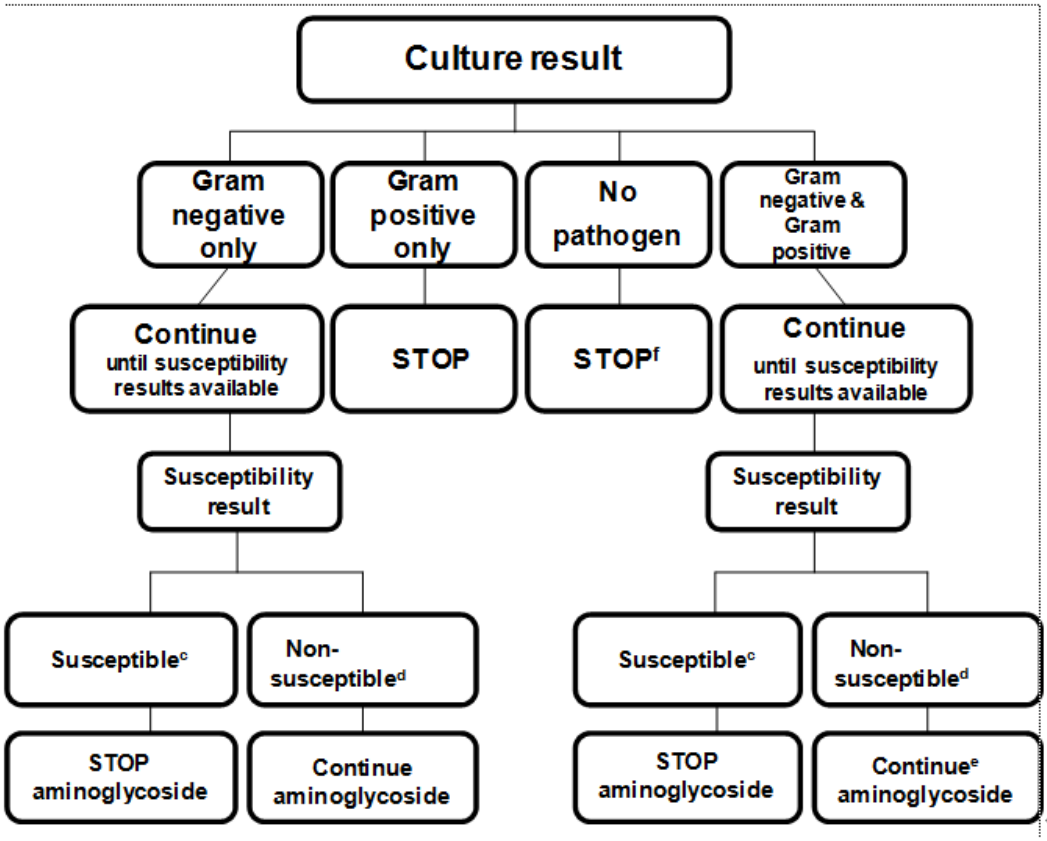
- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 days or more
- Hospitalization for 2 days or more in the preceding 90 days (excluding current hospitalization)
- Residence in a nursing home or extended care facility

Dosing of amikacin refer to pakage insert. The CrCL should be measured daily and dose adjusted appropriately.

Amikacin should be continued for 48 hours and then stopped or continued based on pathogen identification and carbapenem susceptibility results as outlined in Figure 3. If final baseline culture and carbapenem susceptibility results are not available at 48 hours, amikacin use may be extended an additional 24 hours such that a participant may receive a maximum of 72 hours of total amikacin therapy. If a carbapenem non-susceptible Gram-negative pathogen has not been identified at 72 hours, amikacin should be stopped (see Figure 3).

For participants in whom amikacin continuation is indicated, the duration of therapy is at the discretion of the investigator, but cannot be longer than duration of study intervention. Study intervention with CAZ-AVI should continue for 7-14 days, regardless of the need for ongoing amikacin therapy.

Figure 3. Algorithm for Stopping or Continuing Open-lable Empiric Gram-negative Coverage With Amikacin Based on Baseline Culture Results and Susceptibility Results at 48 Hours[a,b]



a. For details regarding use of study intervention see Section 6.1.1.

b. If cultures and susceptibility results are not available at 48 hours, empiric amikacin may be continued for an additional 24 hours (ie 72 hours of total therapy).

c. For participants in whom all Gram-negative pathogens are susceptible to meropenem, imipenem based on local susceptibility results using local interpretive criteria.

d. For participants in whom at least one Gram-negative pathogen is non-susceptible to meropenem, imipenem or doripenem based on local susceptibility results using local interpretive criteria.

e. If the investigator considers the carbapenem non-susceptible Gram-negative organism(s) to be a colonizer which does not warrant treatment, empiric Gram-negative treatment with amikacin may be stopped.

f. When no pathogen is identified, the participant will continue to receive CAZ-AVI and therefore, discontinuation of amikacin is strongly encouraged. However, in certain circumstances it would be acceptable to continue the amikacin if the investigator feels it is in the best interest of the participant. Reasons for continuing amikacin in this circumstance should be documented.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers and in accordance with the labels.

6. See the IP manual for storage conditions of the study intervention once reconstituted and/or diluted.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the Investigational Product Accountability Log (IPAL) or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label, single arm study. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

6.4. Study Intervention Compliance

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

The qualified study center personnel at the study center will administer IV study intervention and treatment compliance will be assured. The dose, date, and exact start and stop time of administration of the IV study intervention will be recorded and checked by the monitor at monitoring visits.

6.5. Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

All prescription and over the counter medications, including herbal products and blood or other blood product transfusions, being taken by the participant from signed informed consent prior to registration (considered prior medications) and from registration through the FPFU visit (considered concomitant medications) must be documented on the appropriate pages of the electronic case report form (eCRF). Systemic antibiotics should be documented for the entire duration of the study (from 2 weeks prior to study entry through the FPFU visit).

The use of probenecid or chloramphenicol and any systemic antibiotic not specified by this protocol is not permitted after registration.

The use of systemic antibiotics not specified by this protocol is not permitted after enrollment. The use of metronidazole (or any other antibiotic active solely against anaerobes) or oral vancomycin (or any other oral antibiotic that is not absorbed systemically) are considered acceptable.

Other medication, which is considered necessary for the participant's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. Should a participant require immunosuppressive agents or chemotherapy after being enrolled to IV study intervention, the investigator should contact the Pfizer physician before initiating therapy. Continued receipt of study intervention will be determined based upon assessment of the safety risk to the participant. Participants should remain in the study and complete all scheduled protocol assessments.

Any participant planning to undergo surgical treatment not compatible with the aims of the study must not be enrolled. For participants who need to undergo a unplanned surgical procedure during the study, the reason for the surgery must be documented as an AE in the eCRF.

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with CAZ-AVI; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

For participants with moderate and severe renal impairment, will require dose modification which are outlined in Table 1.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Stopping criteria for individual participants include:

- In the absence of any alternative explanation for an increase in the following abnormalities, individual participants should be withdrawn if the following criteria are met (see also Appendix 5):
  - ALT or AST >8 × ULN
  - ALT or AST >3 × ULN and either total bilirubin >2 × ULN or evidence of coagulopathy. Evidence of coagulopathy should be discussed with the Pfizer clinician where possible
  - ALT or AST >3 × ULN and with appearance of symptoms suggestive of new or progressive liver disease. Symptoms suggestive of new or

progressive liver disease should be discussed with the Pfizer clinician where possible

- Positive pregnancy test at any time during the study treatment period

Investigators should not discontinue a participant from study intervention on the basis of microbiologic results alone (ie, culture and susceptibility results) without evidence of failure. However, the investigator should frequently re-assess the risk/benefit ratio to the participant as additional data become available during the study.

For participants who discontinue study intervention early, all subsequent scheduled assessments should be collected. The EOT visit should occur within 24 hours of study intervention discontinuation.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Participant or legally recongnized representative decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event (eg, risk to participant, as judged by the investigator or Pfizer)
- Severe noncompliance to study protocol, as judged by the investigator and/or Pfizer
- Treatment failure
- In the opinion of the investigator, it is not in the best interest of the participant to continue the IV study intervention or at the request of Pfizer that the particant stops participation.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;

- Lost to follow-up;
- Death;
- Study terminated by sponsor;

The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the

investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 135 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. Clinical response

To estimate clinical response to CAZ-AVI in HAP patients is the primary objective of this study. A clinical response assessment outcome will be assigned to each participant by the investigator at the EOT and TOC visits. Clinical response outcomes are success, failure and indeterminate, the definitions of which are respectively given in Table 2 and Table 3 for the EOT and TOC visits.

Table 2. Definitions of Clinical Response at the EOT Visit

Clinical response	Definition
Clinical Cure	Participants will be considered to be a success for clinical response if: • The participant is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for HAP/VAP are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for HAP prior to EOT.
Clinical Failure	Participants who meet any 1 of the following criteria will be considered to be a treatment failure for clinical response: • Mortality due to HAP/VAP between Day 3 of study intervention and the EOT visit inclusive. • Incomplete clinical resolution or worsening of HAP-specific signs and symptoms that requires additional antibacterial therapy for HAP at or before EOT. • Development of infectious complications of pneumonia such as empyema or lung abscess after Day 2.
Indeterminate	Participants who meet any 1 of the following criteria will be considered to be indeterminate for clinical response: • Participant lost-to-follow-up or assessment is not undertaken, such that a determination of clinical response cannot be made. • Death on or before the date of the EOT visit where HAP is clearly non-contributory. • Death on study Day 1 or Day 2. • Identification of an infectious complication of pneumonia such as empyema or lung abscess between Day 1 and Day 2 inclusive.

Table 3. Definitions of Clinical Response at the TOC Visit

Clinical response	Definition
Clinical Cure	Participants will be considered to be a success for clinical response if: • The participant was not a clinical failure at EOT, and the participant is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for HAP was taken between EOT and TOC inclusive.
Clinical Failure	Participants who meet any 1 of the following criteria will be considered to be a treatment failure for clinical response: • Designated as a clinical failure at an earlier time point (eg, EOT). • Mortality due to HAP between Day 3 of study intervention and the TOC visit inclusive. • Persistence, incomplete clinical resolution, worsening or recrudescence of HAP-specific signs and symptoms that requires initiation of antibacterial therapy for HAP between EOT and TOC, inclusive.

Table 3. Definitions of Clinical Response at the TOC Visit

Clinical response	Definition
	• Development of complications of HAP such as empyema or lung abscess at or before the TOC visit.
Indeterminate	Participants who meet any 1 of the following criteria will be considered to be indeterminate for clinical response: • Participant lost-to-follow-up on or before the TOC visit or the assessment is not undertaken, such that a determination of clinical response cannot be made. • Death on or before the date of TOC visit where HAP is clearly non-contributory. • Death on study Day 1or Day 2 inclusive. • Identification of an an infectious complication of pneumonia such as empyema or lung abscess between Day 1 and Day 2 inclusive.

8.1.2. Microbiology assessments

All microbiological assessments will be initiated at the local laboratory for specimen collection, shipment of isolates, and analysis of isolates according to the sections below and as outlined in more detail in the microbiology laboratory manual. All respiratory and blood pathogens must be shipped to the central reference laboratory for confirmation of microbiological assessments. A unstained Gram stain slide of each respiratory specimen must also be sent to the central reference laboratory.

All specimens should be processed according to recognized methods that culture for aerobic organisms[8] following the standard operating procedures of the clinical microbiology laboratory at each study center. All cultured pathogens should be kept by the local laboratory at –20°C or colder (preferably at -70°C) until the end of the study or when contacted by the central reference laboratory.

8.1.2.1. Specimen collection

Respiratory specimens

Baseline respiratory cultures must be obtained within 48 hours prior to Day 1 and after development of signs and symptoms of HAP (ideally before receipt of any systemic antibiotics). An adequate and appropriate baseline respiratory culture specimen should be sent to the local laboratory for Gram stain, culture, identification, and in vitro susceptibility testing.

Appropriate specimens from ventilated participants include:

- endotracheal aspirate
- bronchalveoloar lavage (BAL)

- mini BAL
- Protected Brush Specimen (PBS) sample

Appropriate specimens from non-ventilated participants include:

- expectorated or induced sputum
- BAL
- mini BAL
- PBS sample

Note that there may be non-ventilated participants who develop HAP and subsequently require intubation and mechanical ventilation. If such participants require ventilation prior to Day 1, a specimen appropriate for the participant should be obtained even if the participant has already provided a sputum sample. In addition, participants undergoing bronchoscopy prior to Day 1 should provide a respiratory specimen during the procedure even if a sputum sample or endotracheal aspirate has already been obtained.

In the circumstances where more than one culture has been obtained after the onset of signs and symptoms of pneumonia in the 48 hours prior to Day 1, the baseline culture will be established as described in Section 8.1.2.2.

To be considered adequate, respiratory samples from expectorated or induced sputum must show <10 squamous epithelial cells and >25 polymorphonuclear neutrophils per 100 × field upon a Gram stain.

When clinically indicated, pleural fluid should be sampled for Gram stain, culture identification, in vitro susceptibility testing; isolates should be sent to the central laboratory for confirmation. Additionally, (when indicated) cell counts, pH and lactate dehydrogenase (LDH) of pleural fluid as well as serum LDH should also be obtained. It is not necessary to submit a Gram-stain slide of pleural fluid to the central lab.

If treatment is discontinued early because the participant is failing therapy or other reasons, an appropriate respiratory specimen for culture should be obtained, ideally after stopping the initial treatment but before the new treatment is administered. The eCRF should indicate whether or not a sample was obtained.

Blood specimens

Two sets of blood cultures should be collected (ie, 4 bottles) from different sites for aerobic and anaerobic incubation within 24 hours prior to Day 1. Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. One set of blood cultures should be obtained through a venipuncture. Organisms isolated in the blood at study entry will be assigned a microbiologic response similar to those given for pathogens isolated from

respiratory specimens (see Table 4 for list of response categories). If participants are bacteremic, repeat samples must be collected at least every 3 days until clearance of bacteremia has been documented. If repeat cultures have not been finalized negative by the time of the EOT visit, a set of repeat blood cultures should be obtained at the EOT visit. Blood cultures should also be obtained as clinically indicated. Details concerning the collection of blood cultures are provided in the microbiology laboratory manual.

8.1.2.2. Defining the baseline respiratory specimen

In some circumstances, participants may have multiple respiratory specimens obtained after the onset of signs and symptoms of pneumonia in the 48 hours prior to Day 1.

The baseline respiratory culture is defined as the last respiratory culture obtained via BAL, mini BAL or PBS prior to Day 1. If BAL, mini BAL or PBS specimens are not available, the baseline respiratory culture will be defined as the last respiratory culture obtained via endotracheal aspirate prior to Day 1. If none of these are available, the baseline culture is defined as the last sputum culture obtained prior to Day 1.

The status and/or results of the baseline respiratory culture (ie, whether the results are pending or known; pathogen(s) identification and/or the susceptibility profile of the identified pathogens) should be used to determine whether the protocol requirements for empiric Gram-positive or Gram-negative agents have been met as described in Section 6.1.1. Only baseline cultures should be used for determining the need for these agents.

8.1.2.3. Microbiological response definitions

The per-patient and per-pathogen microbiologic response of CAZ-AVI in the mMITT analysis sets at the the EOT and TOC visits is a secondary objective of this study.

Microbiological response will be assessed per-pathogen and per-patient according to the definitions listed in Sections 8.1.2.3.1 and 8.1.2.3.2, respectively. Microbiological outcome per-patient is based on outcome per-pathogen isolated at the initial visit (considered as causative) and on the isolation of pathogens during the course of treatment or the post-treatment period.

8.1.2.3.1. Per-pathogen microbiological assessments

Microbiological response will be assessed separately for each pathogen after completion of all follow-up visits using the definitions listed in Table 4.

Microbiological responses other than “indeterminate” will be classified as “favorable” or “unfavorable”. Favorable microbiological response assessments include “eradication” and “presumed eradication”. Unfavorable microbiological response assessments include “persistence” “persistence with increasing MIC” and “presumed persistence”. “Superinfection” and “new infection” will be considered separately.

8.1.2.3.2. Per-patient (overall) microbiological response assessments

Overall microbiological response will also be assessed as "favorable" or "unfavorable" for each participant. For participants from whom only 1 causative pathogen is isolated, the overall microbiological response assessment will be based on the microbiological response assessment for that pathogen.

For participants from whom more than 1 baseline pathogen is isolated, the overall microbiological response assessment will be "favorable" only if the microbiological response assessment for each of the baseline pathogens isolated is "favorable". The overall microbiological response assessment will be "unfavorable" if at least 1 of the microbiological response assessments is "unfavorable".

8.1.2.3.3. Microbiological response

Each baseline pathogen will be categorized according to the definitions in Table 4.

Table 4. Microbiological Response Categories

Microbiological response	Definition
Eradication	An adequate source specimen demonstrates absence of the original baseline pathogen.
Presumed eradication	An adequate source specimen was not available to culture and the participant was assessed as a clinical cure.
Persistence - Persistence with increasing MIC	Adequate source specimen demonstrates continued presence of the original baseline pathogen. Continued presence of the causative organism in a culture of the respiratory infection obtained during or upon completion of treatment with IV study intervention, and the pathogen that was susceptible to IV study intervention pre-treatment displays a ≥4-fold higher MIC to IV study intervention after treatment with IV study intervention.
Presumed persistence	An adequate source specimen was not available to culture and the participant was assessed as a clinical failure.
Indeterminate	An adequate source specimen was not available to culture and the participant's clinical response was assessed as indeterminate.

Microbiologic response for blood pathogens should be classified similarly to the classifications for baseline pathogens noted in Table 4.

8.1.2.3.4. MIC among pathogens

The favorable per-pathogen microbiologic response at the EOT and TOC visits will be evaluated for MIC categories. The MIC categories to be used are: ≤0.008, 0.015, 0.03, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and >256 µg/mL.

8.1.2.3.5. Emergent infections

Pathogens first appearing after baseline in participants with a baseline pathogen are categorised in Table 5 and will be summarised separately.

Table 5. Emergent Infections

Emergent infection	Definition
Super-infection	Emergence of new pathogen from an adequate respiratory specimen during treatment with study intervention associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics.
New infection	Emergence of new pathogen from an adequate respiratory specimen after completion of study intervention associated with emergence or worsening of signs and symptoms of infection and a requirement for additional antibiotics.
Colonization	Isolation of an organism from an adequate respiratory specimen which is not associated with signs and symptoms of active infection, and does not require antimicrobial therapy.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. If the participant's actual height and weight are not available, the height and weight may be estimated for study use. All height and weight measurements should be recorded in the CRF as actual or estimated.

A brief physical examination will include, at a minimum, assessments of the lungs.Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Tympanic or axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 1 blood pressure measurements.

8.2.3. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.4. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second pregnancy test will be required at the baseline visit prior the participant’s receiving the CAZ-AVI. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant or legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon

awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1. will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until a minimum of 28 calendar days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in

the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with HAP, including VAP, and can be serious/life threatening:

- Disease progression;

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the corresponding CRF page in the participant's CRF within 24 hours

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Not Applicable.

8.3.8.1. Lack of Efficacy

Not Applicable.

8.3.9. Medical Device Deficiencies

Not Applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of CAZ-AVI greater than specified in protocol in Section 6.1.1.1 will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of CAZ-AVI (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic (PK) parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

For the primary efficacy objective and the secondary efficacy objectives, except for estimating all-cause mortality, a composite estimand strategy will be used; for the secondary efficacy objective of estimating all-cause mortality, a treatment-policy estimand strategy will be used.

Primary Efficacy Estimand:

A composite estimand strategy will be used to estimate the clinical response rate at the TOC visit in participants who meet minimum disease requirements (excluding participants not expected to respond to CAZ-AVI). Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before TOC visit where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering treatment with further antibiotics will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and TOC visit inclusive, development of infectious complications of pneumonia after Day 2 until TOC visit triggering treatment with further antibiotics will be regarded as failure clinical response.

Secondary Efficacy Estimands:

- To estimate clinical response to CAZ-AVI in HAP participants, and HAP participants with demonstrated Gram-negative pathogens:

  A composite estimand strategy will be used to estimate the clinical response rate at the EOT visit in participants who meet minimum disease requirements, and at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens (excluding participants not expected to respond to CAZ-AVI for both target populations). Clinical response will be categorized as cure, failure, and indeterminate per investigator's assessment. Intercurrent events of death on study Day 1 or Day 2, death on or before EOT visit (or TOC visit accordingly) where HAP is clearly non-contributory, identification of an infectious complication of pneumonia between Day 1 and Day 2 inclusive triggering further antibiotics treatment will be regarded as indeterminate clinical response. Intercurrent events of death between Day 3 and EOT visit (or TOC visit accordingly) inclusive, development of infectious complications of pneumonia after Day 2 triggering further antibiotics treatment will be regarded as failure clinical response.

- To estimate the microbiologic response to CAZ-AVI:

  A composite estimand strategy will be used to estimate the per-patient and per-pathogen microbiological response rate at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens. Microbiological response will be categorized as favorable (ie, eradication, or presumed eradication), unfavorable (persistence, persistence with increasing MIC, or presumed persistence), and indeterminate. Per-pathogen microbiological response will be summarized with the proportion of participants achieving favorable response by baseline pathogen type; per-patient microbiological response will be summarized with the proportion of participants achieving overall favorable response (ie, favorable for each of the baseline pathogen isolate). Intercurrent events of death or identification of an infectious complication of pneumonia triggering further antibiotics treatment such that an adequate source specimen is not available to culture will be regarded as an indeterminate microbiological response if clinical response is indeterminate, and will be regarded as a presumed eradication if a clinical cure is assessed.

- To estimate the efficacy of CAZ-AVI in participants with pathogens resistant to ceftazidime:

  Same composite estimand strategy as the primary estimand and aforementioned secondary estimands to estimate the proportion of participants with clinical cure and with favorable per-patient microbiological response at the EOT and TOC visits in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens that are resistant to ceftazidime.

- To estimate all-cause mortality for CAZ-AVI:

  A treatment-policy estimand strategy will be used in participants who meet minimum disease requirements, and in participants who meet minimum disease requirements and have demonstrated Gram-negative pathogens to estimate the proportion of participants with death at the TOC visit and Day 28 of the study. Any death that occurred after first dose of study intervention through the nominal analysis timepoint will be included. A participant with the last known survival status that is before the nominal analysis timepoint or missing at the nominal analysis timepoint will be reported as an unknown status.

9.1.2. Hypothesis

There are no formal hypothesis tests planned for this study.

9.2. Sample Size Determination

According to the enrollment experience of the previously completed Phase 3 HAP/VAP study (REPROVE) and feasibility assessment, and considering the enrollment window and number of research centers that may participate, it is estimated that approximately 235 patients will be enrolled. Assuming a 17% data loss rate based on previous clinical study

experience, approximately 200 patients are expected to be evaluable for clinical cure rate in the cMITT population.

Below table shows the precision (ie, 95% confidence interval) with 200 evaluable patients assuming the observed clinical response rate ranging from 60% to 75%.

Evaluable Number	Clinical Cure Rate	95% Confidence Interval (CI)	Half Width of the 95% CI
200	60%	(53.2%, 66.8%)	6.8%
200	65%	(58.4%, 71.6%)	6.6%
200	70%	(63.6%, 76.4%)	6.4%
200	75%	(69.0%, 81.0%)	6.0%

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant / Defined Analysis Set	Description
Enrolled assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Modified Intent-to-Treat (MITT) Analysis Set	It will consist of all enrolled patients who have minimum disease criteria and receive any amount of study intervention.
clinical Modified Intent-to-Treat (cMITT) Analysis Set	This is a subset of the MITT analysis set, and will include participants: • whose (properly obtained) baseline respiratory or blood cultures demonstrate Gram-negative pathogens with or without concomitant Gram-positive pathogens (excluding patients with Gram-negative pathogens not expected to respond to either study intervention [ie, participants with only the following monomicrobial Gram negative infections: any of the *Acinetobacter* species; or any *Legionella* species; or *Stenotrophomonas maltophilia*; or *Elizabethkingia meningoseptica*]); OR • participants in whom no etiologic pathogens are identified from respiratory or blood cultures at baseline.
microbiological Modified Intent-to-Treat (mMITT) Analysis Set	It is a subset of the MITT analysis set, and will include participants: who have a properly obtained respiratory culture demonstrating Gram-negative pathogens, excluding patients not expected to respond to CAZ-AVI (ie, patients with only the following monomicrobial Gram-negative infections: any of the *Acinetobacter* species; or any *Legionella* species; or *Stenotrophomonas maltophilia*; or *Elizabethkingia meningoseptica*). If baseline respiratory cultures are not available or do not identify a respiratory pathogen, but a Gram-negative organism known to cause pneumonia is identified from baseline blood cultures, the participant will qualify for the mMITT population.
Safety Analysis Set (SAS)	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

This is an estimation study. The clinical response, micobiological response and all-cause mortality from participants treated with CAZ-AVI will be estimated at different visit time points and in various analysis populations. The corresponding 95% CIs for the response rates will be calculated.

9.4.2. Primary Endpoint(s)

The number and percent of participants having clinical cure, failure, and indeterminate at TOC visit in the cMITT analysis population will be summarized. Responses missing at the analysis visit such as due to intercurrent events, loss to follow up, early discontinuation will follow the details stated in Section 8.1.1. Clincial cure rate and the corresponding 2-sided 95% CI will be provided.

Results will be listed together with the Phase 3 clinical study REPROVE to observe the consistency trend.

Subgroup analyses will be performed by demographics and baseline disease characteristics such as APACHE II score, systemic antibiotics use, type of microbial infection, bacteremic.

The subgroup results will be compared with same subgroups in the REPROVE study. Due to different study times, operations, drug resistance, etc, the comparisons of results between this study and REPROVE study will not be subject to statistical comparison.

9.4.3. Secondary Endpoint(s)

Same analysis as the primary efficacy endpoint will be performed for the secondary efficacy endpoints. In particular, clinical cure rate, microbiological favorable response (per-patient and per-pathogen), and all-cause mortality will be summarized by number of participants (n), proportion of participants with corresponding 2-sided 95% CI.

9.4.4. Safety Analyses

All safety analyses will be performed on the safety population. These will be presented in tabular and/or graphical format and summarized descriptively and will follow Pfizer standards as appropriate.

The MedDRA coding system will be used to classify all AEs with respect to system organ class and preferred term. All causality and treatment-related, Treatment-emergent AEs, discontinuation due to AEs and laboratory data abnormalities will be summarized with frequency and percentages.

Absolute and change from baseline in selected laboratory tests and vital signs will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. Number and percentages of participants meeting the categorical criteria of laboratory abnormality will be presented.

9.4.5. Other Analyse(s)

None.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant’s participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The

contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 6. Protocol Required Safety Laboratory Assessments

Hematology	Coagulation	Chemistry	Urinalysis[a]	Arterial blood gas[c]	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Partial thromboplastin time Prothrombin time International normalized ratio (INR)	BUN/BU and creatinine Glucose (non-fasting) Calcium Sodium Potassium Chloride HCO_3 / CO_2-CP[f] AST ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy and culture[b]	Arterial pH Partial pressure of oxygen (PaO_2) Partial pressure of carbon dioxide ($PaCO_2$) Oxygen saturation Bicarbonate (HCO_3)	At screening only: • FSH[d] • Pregnancy test (β-hCG)[e]

a. Urinalysis is for screening purposes only.

b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

c. Required for ventilated participants; recommended for non-ventilated participants.

d. For confirmation of postmenopausal status only. High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

e. Serum or urine β-hCG for female participants of childbearing potential.

f. HCO_3 or CO_2-CP results in blood chemistry will be assessed only for those participants at sites which can perform the HCO_3 or CO_2-CP tests.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any untoward medical occurrence that, at any dose:

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical

terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) :

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

- OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
  - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
  - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: APACHE II Classification System

APACHE II SCORE FORM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
1. Temperature (°C)	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
2. Mean arterial pressure (mm Hg)	≥160	130–159	110–129		70–109		50–69		≤49
3. Heart rate (ventricular response)	≥180	140–179	110–139		70–109		55–69	40–54	≤39
4. Respiratory rate (non-ventilated or ventilated)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
5. Oxygenation A-aDO_2 or PaO_2 (mm Hg) a) FiO_2 ≥0.5:record A-aDO_2	≥500	350–499	200–349		<200				
b) FiO_2 <0.5:record only PaO_2					>70	61–70		55–60	<55
6. Arterial pH – If no ABGs record Serum HCO_3 below	≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
7. Serum Sodium (mmol/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
8. Serum Potassium (mmol/L)	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
9. Serum Creatinine (mg/dL) Double points for acute renal failure	≥3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
10. Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
11. White Blood Count (k/mm^3)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
12. Glasgow Coma Scale (Score = 15 minus actual GCS)	15 – GCS=								
A. Total Acute Physiology Score (APS)	Sum of the 12 individual points =								
* Serum HCO_3 (venous-mmol/L) Not preferred, use if no ABGs	≥52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15

Glasgow Coma Scale	(Circle appropriate response)	**B Age**	**Points**	**C**	Chronic Health Points	**Apache-II Score** (sum of A+B+C)
Eyes open	verbal - nonintubated	Age	Points		If any of the 5 CHE categories is answered yes	
4 - spontaneously	5 - oriented	<=44	0		give +5 points for non-operative or emergency	A APS points
3 - to speech	4 - confused	45-54	2		postoperative patient and give +2 points if	+ B Age points
2 - to pain	3 - inappropriate words	55-64	3		elective postoperative patient	+ C Chronic Health Points
1 - no response	2 - incomprehensible sounds	65-74	5			_____
	1 - no response	>=75	6	Liver	Cirrhosis with PHT or encephalopathy	= Total Apache II
Motor response				CV	Class IV angina or at rest or with minimal self	
6 - to verbal command	verbal - intubated	**Age points =**			care activities	
5 - localizes to pain	5 - seems able to talk			Pulmonary	Chronic hypoxemia or hypercapnia or	
4 - withdraws to pain	3 - questionable ability to talk				polycytaemia of PHT > 40mmHg	
3 – flexion to pain	1 - generally unresponsive			Kidney	Chronic peritoneal or hemodialysis	
2 – extension to pain				Immune	Immune compromised host	
1 - no response					**Chronic Health Points =**	

Abbreviations: ABGs = arterial blood gases; CHP = Chronic Health Points; CV = cardiovascular; GCS = Glasgow Coma Score; PHT = pulmonary hypertension.

APACHE II Score Worksheet:

- Abstract data from the 24 hour interval prior to baseline.
- Enter the value for each line item. Calculate APACHE II score using most recent local laboratory results.

APACHE II Worksheet instruction

A - Physiological components

- Document one score for each of the physiological variables. Then calculate and document the total APS.
- The following will be accepted as core temperatures: rectal, esophageal, bladder, tympanic, or central. If the only temperature data available is from the oral or axillary routes, convert the temperature to an APACHE II core value using the following conversion factors:
  - Actual oral temperature (°C) + 0.5°C= Rectal (core) temperature;

- Actual axillary temperature (°C) + 1.0°C = Rectal (core) temperature.

- For the MAP value, use arterial line data if available, otherwise calculate the MAP from the cuff pressure using the following formula:

  MAP = 1/3 (SBP – diastolic blood pressure [DBP]) + DBP

  (Example: BP 90/60, MAP = 1/3 (90 - 60) + 60 = 10 + 60 = 70)

  Note: If a DBP was not obtained, do not calculate a MAP, record "not done".

- Oxygenation
  - in case the FiO_2 is >50%, calculate the alveolo-arterial oxygen difference ($A\text{-}aDO_2$) using the following formula, use ABGs results:

    $A\text{-}aDO_2$=[(FiO_2 (713)-(partial pressure of carbondioxide ($PaCO_2$)/0.8)] - PaO_2

    (Example: FiO_2=0.6; PaO_2=56; and $PaCO_2$=26

    (0.6 x 713) minus (26 : 0.8) minus 56

    427 - 32.5 = 395.3 - 56 = 339.3 = $A\text{-}aDO_2$ (mm Hg)

    To calculate use FiO_2 (in decimal), $PaCO_2$ (mm Hg) and PaO_2 (mm Hg).

  - If the FiO_2 is <50%, record the lowest PaO_2.
  - In case there is no ABG available assume normal oxygenation (Variable score = 0).
- Serum creatinine (µmol/L): double point score for acute renal failure. Creatinine conversion from µmol/L to mg/dL to be: 88.4 µmol/L= 1 mg/dL.
- WBC Count. Record WBCs in 1000s (eg, a WBC count of 30000 cells/mm^3 would be recorded as 30).

- Arterial PH should be substituted by serum bicarbonate (HCO_3) if there are no ABGs available in the previous 24 hours.

B – Age Points

- Circle the appropriate point for the subjects age range.

C - Chronic Health Points

If the subject has a history of severe organ system insufficiency or is immunocompromised assign chronic health points as follows:

- For nonoperative or emergency postoperative subjects: 5;
- For elective postoperative patients: 2;
- Subject does NOT have a history of severe organ system insufficiency and is NOT immunocompromised: 0.

They will receive the points only once (which means even if they have 2 criteria, the maximum is either 2 or 5).

GLASGOW COMA SCALE

For the GCS score, determine the lowest (worst) number for each of the 3 factors in the scale (eye opening, verbal response, and motor response). Add together these 3 numbers, and then subtract this number from 15 to get the final GCS score. The subject's neurological status during a single neurological assessment should be evaluated.

Since it is not possible to assess the GCS in subjects who are sedated and paralyzed, by convention the GCS is regarded as normal, unless it is known that there was a brain injury prior to sedation. In that case the last measured GCS is to be used; if there is no brain injury prior to sedation the GCS is 15, thus the neurologic score will be 0.

10.7. Appendix 7: Calculation of Estimated Creatinine Clearance

CALCULATION OF THE ESTIMATED CREATININE CLEARANCE

Estimated creatinine clearance will be calculated using the following Cockcroft-Gault formula[9]. The weight obtained at Screening should be used to qualify for entry into the study. In order to determine the need to adjust the dose and/or dosing interval of IV study intervention to be administered, the patient's estimated creatinine clearance must be calculated using the most recent serum creatinine value that was obtained at the local laboratory, the patient's most recent actual (not ideal) body weight, and the Cockcroft-Gault formula.

Cockcroft-Gault formula:

Estimated creatinine clearance is calculated by Cockcroft-Gault as follows:

For serum creatinine in mg/dL:

estimated creatinine clearance = [(140 – age) × weight in kilograms] / [72 × serum creatinine in mg/dL]

(× 0.85 if female)

For serum creatinine in µmol/L:

estimated creatinine clearance = [(140 – age) × weight in kilograms × constant] / [serum creatinine in µmol/L]

where constant = 1.23 for males and 1.04 for females.

10.8. Appendix 8: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
5-HT	serotonin
A-aDO_2	alveolar-arterial oxygen difference
ABGs	arterial blood gases
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
APS	Acute Physiology Score
AST	aspartate aminotransferase
AVI	Avibactam
BAL	bronchalveoloar lavage
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
BU	blood urea
BUN	blood urea nitrogen
CARES	Chinese antimicrobial resistance surveillance of nosocomial infection
CAZ	Ceftazidime
CDAD	*Clostridium difficile* associated diarrhea
CCI	[redacted]
CE	clinical evaluable
CFR	Code of Federal Regulations
CHINET	China surveillance network for bacterial resistance
CHP	Chronic Health Points
CI	confidence intervals
cIAI	complicated intra-abdominal infection
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
cMITT	clinically modified intent-to-treat
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CrCL	creatinine clearance
CRE	carbapenem-resistant Enterobacteriaceae
CRF	case report form
CRO	contract research organization
CRPA	carbapenem-resistant *Pseudomonas aeruginosa*
CSR	clinical study report
CT	computed tomography/clinical trial

Abbreviation	Term
cUTI	complicated urinary tract infection
CXL	ceftaroline-avibactam
CV	cardiovascular
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DRE	disease-related event
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOT	end of treatment
ESBL	extended-spectrum β-lactamases
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FPFU	final protocol follow up
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
GGT	gamma-glutamyl transferase
HAP	Hospital-Acquired Pneumonia
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
ICD	informed consent document
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
KPC	*Klebsiella pneumoniae* carbapenemases
LDH	lactate dehydrogenase
LFT	liver function test
LPD	local product document
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
mMITT	microbiologically modified intent-to-treat
msec	millisecond
MTZ	metronidazole
N/A	Not Applicable
NI	non-inferiority
NIMP	noninvestigational medicinal product
NMPA	the National Medical Products Administration
CCI	[redacted]
PACL	Protocol Administrative Change Letter
PaO_2	partial pressure of oxygen
PBS	Protected Brush Specimen
PK	pharmacokinetic(s)
q8h	every 8 hours
q24h	every 24 hours
Qual	qualitative
RBC	red blood cell
SAE	serious adverse event
SAS	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TOC	test of cure
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential
VAP	Ventilator-Associated Pneumonia

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